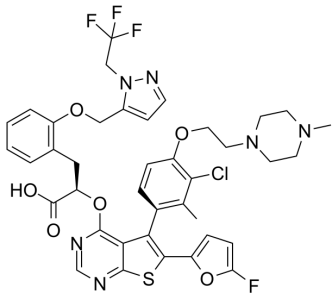
S63845

Cat. No.:	HY-100741
CAS No.:	1799633-27-4
Molecular Formula:	$C_{39}H_{37}ClF_4N_6O_6S$
Molecular Weight:	829
Target:	Bcl-2 Family
Pathway:	Apoptosis
Storage:	4°C, protect from light, stored under nitrogen * In solvent : -80°C, 6 months; -20°C, 1 month (protect from light, stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 33.33 mg/mL (40.21 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.2063 mL	6.0314 mL	12.0627 mL
	5 mM	0.2413 mL	1.2063 mL	2.4125 mL
	10 mM	0.1206 mL	0.6031 mL	1.2063 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 5 mg/mL (6.03 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (2.51 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (2.51 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

S63845 is a potent and selective myeloid cell leukemia 1 (MCL1) inhibitor with a K_d of 0.19 nM for human MCL1[1].

IC_{50} & Target

MCL1
0.19 nM (Kd)

In Vitro

The pro-survival protein myeloid cell leukemia 1 (MCL1) is over expressed in many cancers. S63845 is a small molecule that specifically binds with high affinity to the BH3-binding groove of MCL1. S63845 potently kills MCL1-dependent cancer cells, including multiple myeloma, leukaemia and lymphoma cells, by activating the BAX/BAK-dependent mitochondrial

	apoptotic pathway. The activity of S63845 is next evaluated in a panel of eight AML cell lines: all lines are sensitive to S63845 (IC_{50}=4-233 nM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	S63845 shows potent anti-tumour activity with an acceptable safety margin as a single agent in several cancers. Intravenously injected (i.v.) S63845 exerts dose-dependent anti-tumour activity in human multiple myeloma (H929 and AMO1) xenografts in immunocompromised mice, with maximal tumour growth inhibition of 114% in the AMO1 model and 103% in the H929 model. At 25 mg/kg, S63845 induces complete regression in 7 out of 8 of the mice at 100 days after treatment in the AMO1 model[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	10 mM HEPES pH 7.4, 175 mM NaCl, 25 μM EDTA, 1 mM TCEP, 0.01% P20 and 1% DMSO is used as a running buffer. The ligand surface is generated using double His-tagged proteins. Serial dilutions of the compound in buffer are injected over the protein surface. All sample measurements are performed at a flow rate of 30 μL per min (injection time 120 s, dissociation time 360 s). The sensor surface is regenerated by consecutive injections of 0.35 M EDTA pH 8.0 with 0.1 mg/mL trypsin, 0.5 M imidazole and 45% DMSO (60 s, 15 μL per min)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	Cells are treated with increasing doses of S63845 (typically 0.008, 0.025, 0.04, 0.2, 1, 5 μM) for 24 h. Cells are stained with Annexin V-FITC and propidium iodide, analysed on a FACS Calibur and live cells are recorded. Data are presented as per cent cell death induction relative to cells cultured in medium alone[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice: S63845 is formulated extemporaneously in 25 mM HCl, 20% 2-hydroxy propyl β -cyclo dextrin 20% and administrated at the 6.25, 12.5, 25 mg/kg for 0, 20, 40, 60, 80 days. Tumour growth inhibition (TGImax) is calculated[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2023 Jan;613(7942):187-194.
- Nature. 2021 Mar;591(7850):477-481.
- Cell. 2022 Sep 1;185(18):3356-3374.e22.
- Cell. 2022 Apr 28;185(9):1521-1538.e18.
- Signal Transduct Target Ther. 2023 May 9;8(1):194.

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REFERENCES

[1]. Kotschy A, et al. The MCL1 inhibitor S63845 is tolerable and effective in diverse cancer models. Nature. 2016 Oct 27;538(7626):477-482.

Caution: Product has not been fully validated for medical applications. For research use only.

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